(12) UK Patent Application (19) GB (11) 2 216 795 (13) A

(43) Date of A publication 18.10.1989

(21) Application No 8905843.2

(22) Date of filing 14.03.1989

(30) Priority data
(31) 8806367 (32) 17.03.1988 (33) GB

(51) INT CL⁴
A61K 9/22

(52) UK CL (Edition J)
A5B BNC B832 B835

(56) Documents cited
GB 2153677 A GB 2153676 A US 3279996 A

(58) Field of search
UK CL (Edition J) A5B BLF BLG BLM BNC
INT CL⁴ A61K
DIALOG One Search SM (CAS, WPI, Medicine)

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(54) Controlled release siloxane matrices with non-uniform internal drug distribution

(57) A method for loading an active substance into a siloxane matrix comprises preparing a cross-linked siloxane matrix, loading the cross-linked matrix with an active substance by swelling, and drying the resulting swollen system to give a non-uniform internal distribution of active substance in the matrix. The resulting matrix may be used in pharmaceutical devices such as subcutaneous implants loaded with methyl hydroxy progesterone acetate or other steroids. The release of drug or active substance is characterised by a constant rate, whereas matrices prepared by a reference method show a progressively diminishing rate.

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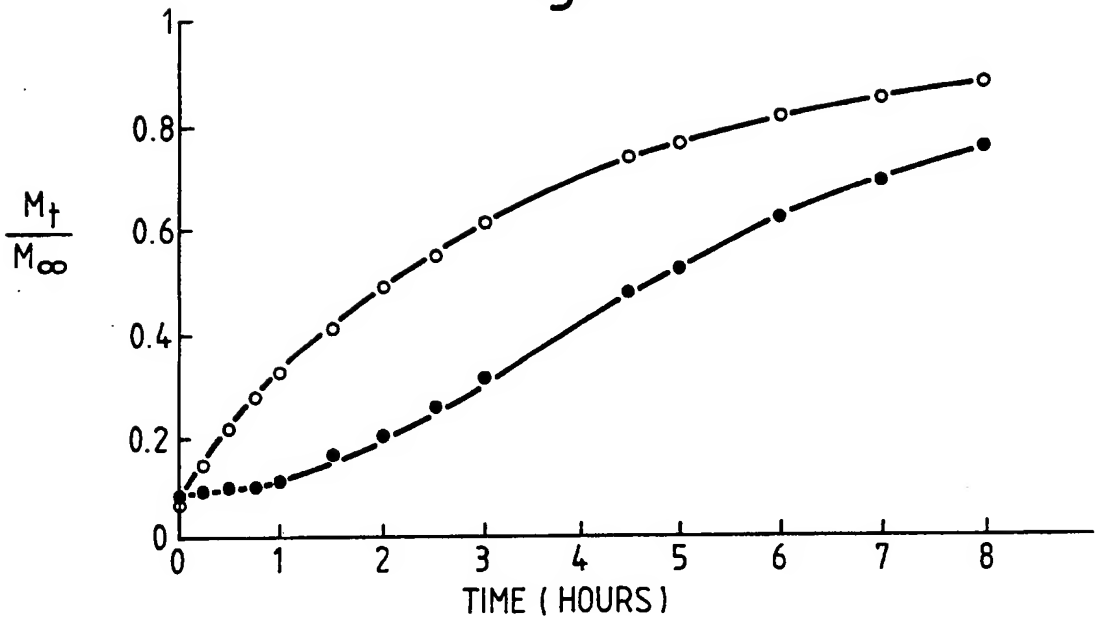
At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.

Fig. 1.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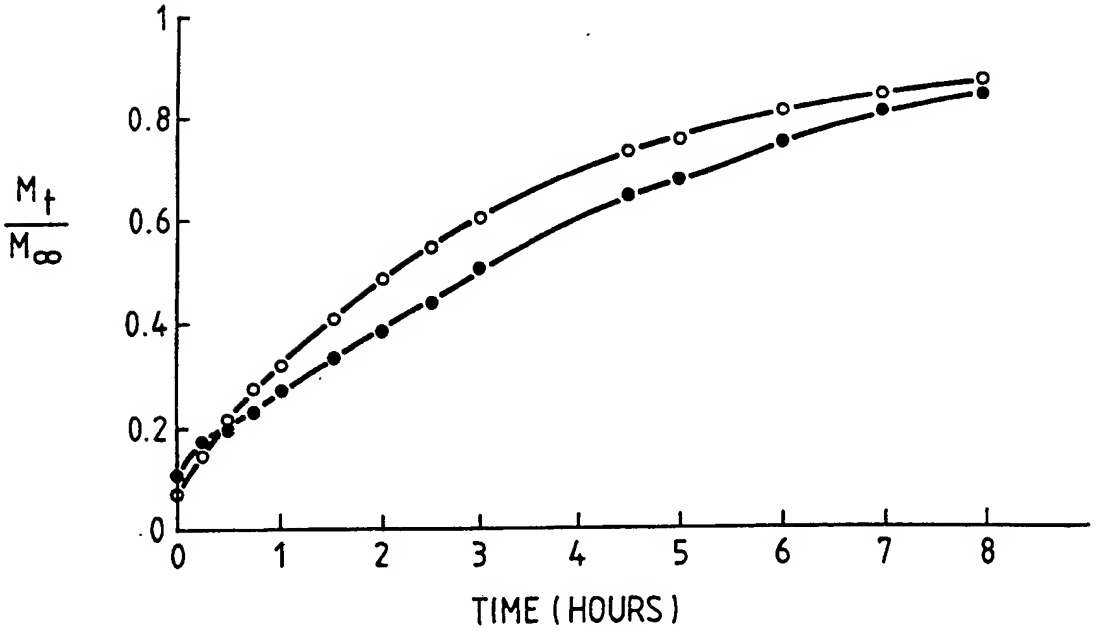
1
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
6
7
8
TIME (HOURS)

Fig. 2.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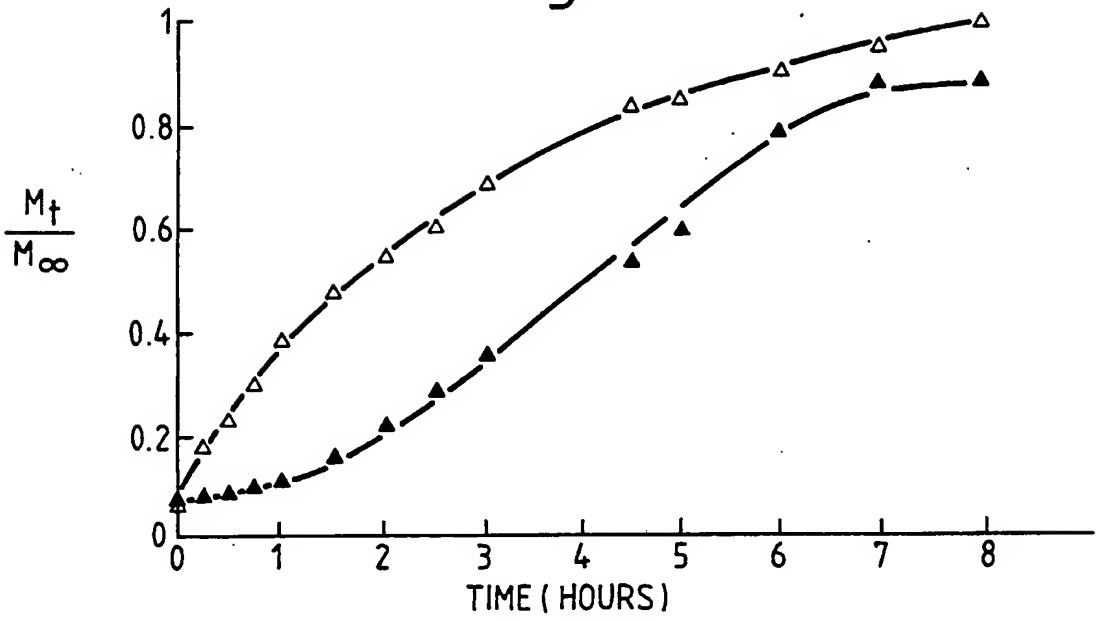
0
0
1
2
3
4
5
6
7
8
TIME (HOURS)

Fig.3.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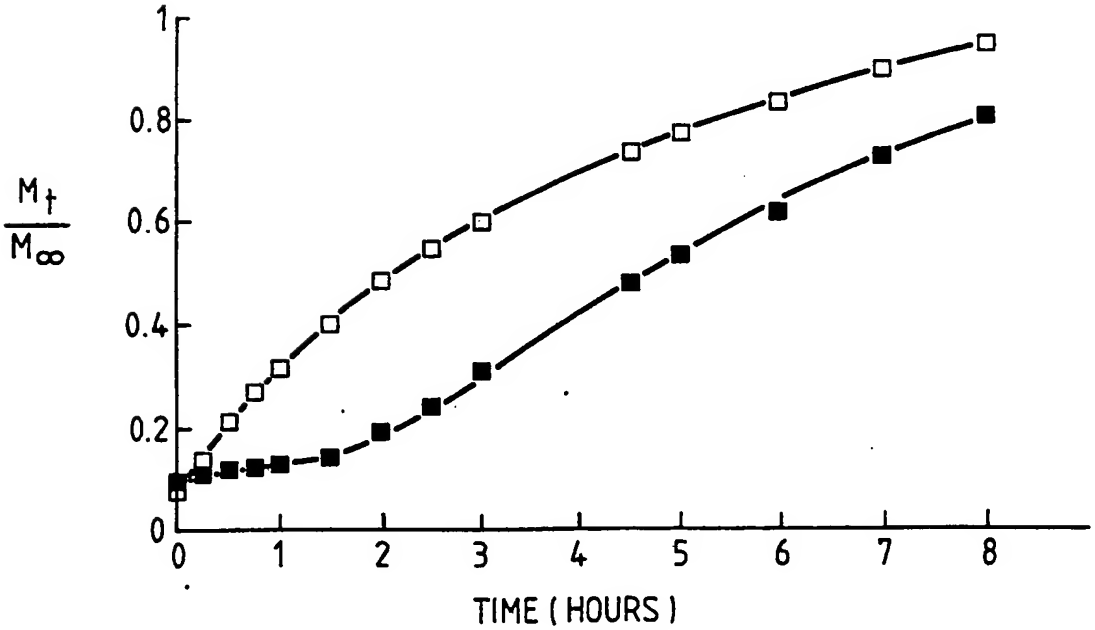
0.4
0.2
0
0 1 2 3 4 5 6 7 8
TIME (HOURS)

Fig.4.


$\frac{M_t}{M_\infty}$
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0.6
0.4
0.2
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0 1 2 3 4 5 6 7 8
TIME (HOURS)

SILOXANE MATRICES WITH INTERNAL NON-UNIFORM DRUG DISTRIBUTION

The present invention covers a method for drug loading into siloxane matrix.

The use of polysiloxane polymers for subcutaneous implants as carriers for the controlled release of drugs dates back to 1966. US-A-3,279,996 describes a method for introducing therapeutic agents into the body before cross-linking and also mentions the possibility of loading by swelling in a solvent. However, no experimental data are given, nor are any specific methods described.

In matrices loaded by mixing with a drug and then cross-linking, the drug is distributed uniformly but for optimized release (constant release kinetics) it is preferable to have a non-uniform distribution of the drug in a non-uniform matrix. The methods proposed till now in order to obtain such distribution have been those of cross-linking in successive molds (US-A-3,920,805 and US-A-4,191,741) with eventual treatment of the washing surface in a solvent GB-A-2136688).

When preparing the matrices by swelling, there has been surprisingly found a non-uniform distribution of the drug inside, that can be controlled by varying the time of swelling and the concentration of the swelling solution and by the drying process parameters. This method may be used as a valid alternative to the method of cross-linking in

concentric molds by simplifying the technology.

Accordingly the invention provides a method for loading a drug into a siloxane matrix which comprises preparing a cross-linked siloxane matrix, loading the cross-linked matrix with a drug by swelling, and drying the resulting swollen system such that a non-uniform internal distribution of the drug in the matrix is achieved.

The siloxane matrix is typically prepared by mixing at least one un-crosslinked siloxane base polymer with a curing agent and allowing the mixture to crosslink. A catalyst is also typically used, optionally with at least one filler and/or at least one additive. Suitably, about 100 parts by weight of the base polymer are mixed with from 10 to 40 parts by weight of the curing agent. The base polymer generally has methylvinylpolysiloxane units and is, for example, Dow Corning MDX-4-4210 Clean Grade Elastomer. The curing agent is typically a polymer having methyldimethylsiloxane units. The catalyst is generally a platinum catalyst and the filler is suitably a silica filler.

The mixture is suitably placed in a mold prior to being allowed to crosslink. The mold may be of any shape but a cylindrical mold is typically used. The mixture is suitably left to crosslink for 20 to 60 hours, for example from 30 to 50 hours. A 48 hour cross-linking time is particularly preferred.

The drug is loaded into the siloxane matrix by swelling. This is generally carried out by immersing the matrix in a solution obtained by dissolving the drug in a solvent.

The swelling solution contains the drug in any appropriate concentration. Typically, the solution contains from 1 to 300mg, for example from 10 to 200mg, of the drug per 100ml of the solvent. Examples of suitable solvents include low boiling solvents, such as solvents having a boiling point from 20°C to 85°C. These are exemplified by methylene chloride and cyclohexane. When methylene chloride is used as solvent a suitable drug concentration is from 30mg/ml to 300mg/ml, for example from 50mg/ml to 100mg/ml.

Suitable swelling times are from 5 minutes to 48 hours, say from 30 minutes to 24 hours. The swelling time more typically is from 1 hour to 24 hours, for example from 3 hours to 24 hours.

When the drug has been loaded into the matrix by swelling, the resulting swollen system is dried. The drying conditions are selected so that the solvent is removed rapidly and efficiently without the active substance being adversely affected, and vary according to the specific drug and solvent used.

Drying is typically carried out under vacuum at a temperature which is generally from 20°C to 80°C, for example from 40°C to 60°C. A temperature from 50°C to 60°C, for example about 55°C, is particularly suitable. Drying

times typically vary from 1 to 10 hours, for example from 2 to 6 hours. A drying time of about 3 hours is generally preferred.

The non-uniform distribution of drug achieved in the loaded siloxane matrix varies according to the concentration of the drug in solution and the pressure, temperature and time of drying the matrix. The concentration of drug in the matrix varies over a wide range. Typically, however, the drug represents from 0.5% to 15%, for example from 3% to 5.5%, by weight of the total weight of the loaded matrix.

The active substance loaded into the matrix in accordance with the present invention is a drug. Typical examples of suitable drugs include steroids, such as megestrol acetate, norgestrel, testosterone, progesterone, estrone and methylhydroxyprogesterone acetate (MAP). In particular, MAP is used. This steroid exhibits progestinic activity at low dosage levels and anti-tumour activity at high dosage levels.

The matrix used in the invention is typically cylindrical, this shape being particularly convenient for the various applications envisaged for the drug release system. The cylinder may have any dimensions, but typically has a length from 0.5cm to 3cm, for example about 2cm. The diameter is suitably from 5mm to 15mm, for example from 8mm to 12mm. A diameter of 10mm is especially preferred.

The process of swelling the matrix in a solution of active substance results in the formation of two separate

"zones"; an external zone depleted in crystalline active substance, and an internal zone, or inner core, comprising the active substance distributed non-uniformly. The distribution achieved in the inner core is a function of the concentration of the swelling solution, the time of swelling and the percentage of curing agent in the matrix. The matrix produced as described above allows the drug with which it is loaded to be released at a constant rate over a period of time in any animal or human to whom it is administered. The matrix may be incorporated into a pharmaceutical device or used by itself as an implant. The implant is typically a subcutaneous implant for human or veterinary use comprising a siloxane matrix prepared as described above. The invention also provides a pharmaceutical device comprising a siloxane matrix prepared as described above. The following Examples further illustrate the invention. In the Figures referred to in the Examples:

In Figure 1 and 2 the curves marked ● denote data obtained with a matrix prepared according to the invention by swelling a prior-crosslinked polymer, comprising 40 parts of curing agent, with a solution of MAP in methylene chloride for 24 hours. In Figure 1 the solution used has a concentration of 50mg/ml of MAP and in Figure 2 the solution has a concentration of 100mg/ml. The curves marked to O refer to data obtained with a reference matrix, prepared by mixing a 2.3% solution of MAP directly with the polymer

comprising 20 parts of curing agent and then crosslinking.

In Figure 3 the curve marked ▲ denotes data obtained with a matrix prepared according to the invention by swelling a prior-cross-linked polymer, comprising 20 parts of curing agent, with a 50mg/ml solution of MAP in methylene chloride for 24 hours. The curve marked Δ denotes data obtained with a reference matrix, prepared by mixing a 2.3% solution of MAP directly with the polymer comprising 20 parts of curing agent and then cross-linking.

In Figure 4 the curve marked ■ denotes data obtained with a matrix prepared acccording to the invention by swelling a prior cross-linked polymer, comprising 10 parts of curing agent, with a 50mg/ml solution of MAP in methylene chloride for 24 hours. The curve marked □ refers to data obtained with a reference matrix, prepared by mixing a 2.0% solution of MAP directly with the polymer comprising 10 parts of curing agent and then cross linking.

Preparation of matrices with non-uniform drug distribution

EXAMPLE 1

A polymeric matrix is prepared by mixing for five minutes 100 parts of a base component consisting of a polymer having methylvinylpolysiloxane units (Dow Corning MDX-4-4210 Clean Grade Elastomer), additives, silica fillers and a platinum catalyst and 40 parts of a curing agent consisting of a polymer with methyldimethylsiloxane units.

The mixture is then placed in a cylindrical mold and left to cross-link for 48 hours. The resulting polymeric matrix is immersed in a 50 mg/ml MAP solution in methylene chloride and left for 24 hours and afterwards extracted and dried in a vacuum oven at 55°C under vacuum until complete evaporation of the solvent.

Data describing the drug release of said matrix are reported together with those of a homogeneous reference matrix in Figure 1.

EXAMPLE 2

A cross-linked polymeric matrix is prepared as described in Example 1. The solution used for the loading of the drug is of 100 mg/ml of MAP in methylene chloride. The times of loading and drying are the same as described in Example 1. Data describing the drug release of said matrix are reported, together with those of a homogeneous reference matrix, in Figure 2.

EXAMPLE 3

A polymeric matrix is prepared by mixing 100 parts of base component and 20 parts of "curing agent" and leaving the mixture to cross-link for 48 hours in a cylindrical mold. The matrix so obtained is placed in a 50 mg/ml MAP solution in methylene chloride for 24 hours and then dried at 55°C in a vacuum oven under vacuum.

Data describing the drug release of said matrix are

reported, together with those of a homogeneous reference matrix, in Figure 3.

EXAMPLE 4

A polymeric matrix is prepared by adding 100 parts of base component and 10 parts of "curing agent", placing the mixture in a cylindrical mold and leaving it as described in the previous examples for 48 hours to cross-link. The matrix then is placed in 50 mg/ml MAP solution in methylene chloride during 24 hours and dried in a vacuum oven at 55°C under vacuum. Data describing the drug release of said matrix are reported, together with those of a homogeneous reference matrix, in Figure 4.

Preparation of the reference matrices with uniform drug distribution

Polymeric matrices with uniform internal drug distribution are prepared by mixing the base polymer and the "curing-agent" in the amounts used to obtain the matrices described in Examples 1 to 4 and a quantity of drug sufficient to bring up its percentage as near as possible to the one contained in the matrices obtained by swelling. The resulting mixtures are then placed in a cylindric mold and left to cross-link for 48 hours.

Drug release rate data

METHOD

The release kinetics of the drug by the polymeric matrices prepared as described in Examples 1, 2, 3 and 4 are studied by placing the matrices in 50 ml of methylene chloride and stirring at 120 rpm at room temperature, then at fixed times drawing a sample of the solution and restoring the initial volume with solvent. Methylene chloride was used in order to reduce the rate of drug release but was in fact found not to alter the release mechanism.

The concentration of drug in a sample is read using a UV spectrophotometer readable at a l/max 238 rm $E^{1\%}$ 445.8. The results obtained are used to determine the fraction (Mt/M) of drug released at a time t compared with the total loading of drug on the matrix.

The values obtained are shown in Figures 1, 2, 3 and 4 and compared with the data obtained from the release of drug by homogeneous matrices.

RESULTS

As shown in Figures 1 to 4 matrices prepared by swelling of an already cross-linked polysiloxane, exhibit release kinetics very different from those of matrices prepared by mixing a drug with a matrix before cross-linking.

It is apparent from the four examples reported that matrices prepared by swelling a cross-linked matrix provide a nearly constant rate of release of drug over a prolonged period, whereas matrices prepared by the reference method provide, over the whole release interval, a progressively diminishing rate of release (after an initial quick release, the burst effect). Eventually, after a time depending upon the individual matrices, drugs and conditions but usually 24 hours, both types of matrix will release 97 to 98% of the drug load.

These results that have been quite surprisingly found have been attributed to a non-uniform internal distribution of the drug, influenced essentially by the swelling time, by the concentration of the swelling solution and by the drying conditions.

CLAIMS

1. A method for loading a drug into a siloxane matrix, which comprises preparing a cross-linked siloxane matrix, loading the cross-linked matrix with a drug by swelling, and drying the resulting swollen system such that a non-uniform internal distribution of drug in the matrix is achieved.

2. A method according to claim 1 wherein the matrix is a polysiloxane matrix.

3. A method according to claim 1 or 2 wherein the cross-linked matrix is swollen by immersing the matrix in a solution obtained by dissolving the drug in a solvent.

4. A method according to any one of the preceding claims wherein the solvent is methylene chloride.

5. A method according to any one of the preceding claims wherein the drug is methylhydroxyprogesterone acetate.

6. A method according to any one of the preceding claims wherein swelling is carried out for 5 minutes to 48 hours.

7. A method according to any one of the preceding claim wherein drying is carried out under vacuum.

8. A method according to any one of the preceding claims wherein the siloxane matrix comprises methyldimethyl-siloxane units.

9. A method according to Claim 1 and substantially as hereinbefore described in the Examples.

10. A subcutaneous implant for human or veterinary use comprising a siloxane matrix prepared by the method as claimed in any one of the preceding claims.

11. A pharmaceutical device comprising a siloxane matrix prepared by the method as claimed in any one of the preceding claims.

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